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Research Article

A SURVEILLANCE STUDY OF ADVERSE DRUG REACTIONS IN A TERTIARY CARE TEACHING HOSPITAL IN INDIA

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ABSTRACT

Objectives: The present study is undertaken to monitor and analyze the suspected adverse drug reactions reported at tertiary care teaching hospital, to characterize nature and predictability of adverse drug reactions (ADRs), and to identify most common medicines causing ADRs.

Methods: A retrospective observational study was conducted between January 2014 and June 2016. Suspected ADRs were submitted to National Pharmacovigilance Center. Following parameters were studied: Age group-pediatric, adult, geriatric, gender, group wise, system wise classification of ADRs, Most common medicines causing ADRs, Causalty assessment of ADRs by using WHO-UMC causality assessment scale, Assessement of preventability criteria by Schumock and Thornton scale.

Results: During the study period, a total of 1099 ADRs reported were analyzed. Male experienced a significantly higher percentage of ADRs (55.86%). Highest percentage of ADRs was found in adult age group 31–40 years. All ADRs were probable. There was no any certain ADR we could find out. Maximum number of ADRs were in the age group of 31–40 years, i.e., 377 (34.30%). Skin was the most common organ showing highest number of ADRs (41.87%). Internal medicine was the most common department showing 28.33% ADRs. Of total antimicrobial agents causing ADRs, maximum number of ADRs were due to amoxicillin+clavulanic acid. Common symptoms due to ADRs of medicines were itching 174 (15.83%) and skin rash 108 (9.82%).

Conclusion: There is urgent need of promotion of spontaneous reporting of ADRs. More awareness needs to be created to address these issues.

Keywords: Adverse drug reactions, Pharmacovigilance, Causality assessment scale, Thornton and Schumock scale.

INTRODUCTION

According to the WHO, adverse drug reaction (ADR) is defined as "any response which is noxious and unintended and occurs at dosages normally used in humans for prophylaxis, diagnosis, or therapy for disease or for the modification of physiological function" [1]. This includes allergies, idiosyncrasies, pharmacological and toxicological mechanisms, and interactions between medicines and excludes adverse reactions due to drug overdose (poisoning), drug abuse, and therapeutic errors. ADRs may arise as a result of immunological or non-immunological mechanisms [2]. According to Rawlins and Thompsons classification, ADRs are defined as Type A, Type B, Type C, Type D, Type E, Type F, and Type G. Type A reaction is an over enhancement of the normal pharmacology of the medication and is predictable and related to dosage. Type B reaction is unrelated to normal pharmacology and is unpredictable. Type C reaction includes those associated with cumulative exposure to the drug and persists for a longer period of time. Type D reactions consist of delayed reaction of carcinogenesis and teratogenesis. Type E includes end of treatment effects and Type F is failure of therapy, while Type G consists of genetic reaction [3,4].

ADRs are important clinical problems and a constant concern of public health system. The incidence of ADRs in Indian population ranges between 1.8% and 25.1% with 8%, resulting in hospitalization [5]. Commonly prescribed medications such as antimicrobial agents (AMAs), analgesics and anti-inflammatory medicines, hypoglycemic medicines, diuretics, and anticoagulants are responsible for 60–70% of ADRs [6].

To reduce these large percentage of ADRs and to minimize physical, mental, and economical burden over patients because of ADRs, the establishment and assessment of causal relationship with drug to initiate measures to treat the present ADRs have to be done earliest.

In India, a large number of pharmaceutical preparations - branded and generic - are available and there is a common practice of over the counter different systems of health-care traditions, and lack of awareness on rational drug use is expected to produce a high level of drug-induced illness [7]. There is a paucity of ADR data in Indian context, so here the role of pharmacovigilance comes. Pharmacovigilance is a science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problem [8]. Hence, it is worthwhile to detect, assess, and characterize the pattern of ADRs in outpatient departments of tertiary care hospitals.

METHODS

A longitudinal, retrospective, observational study was conducted in patients attending outpatient department from January 2014 to March 2016. All suspected ADRs of patients in the hospital were referred by health-care professionals, and the diagnosis was made by concern doctors. The data were recorded as per spontaneous ADR reporting system [9]. The recorded data were filled in the ADR form obtained from pharmacovigilance program of India (2011) and Central Drug Standard Control Organization website.

Patient's gender, type of ADR, history of diseases, starting date of ADR, suspected drug causing ADR, primary source of ADR, concomitant medicines given, and reporting person's initials (doctor, nurse, resident, physician, and pharmacist) were noted. The data were analyzed; causality assessment was done according to the WHO-UMC causality

assessment scale [10], severity assessment was done by Hartwig–Siegel severity scale, and preventability assessment was performed by modified Thornton and Schumock scale. Respective physician of the institution helped in the process and data were analyzed using simple proportions method.

RESULTS

During the study period, a total of 1099 ADRs reported were analyzed.

Fig. 1 shows gender-wise distribution of ADRs. Male experienced a significantly higher percentage of ADRs (55.86%) than females (44.13%). Male-to-female ratio according to the occurrence of ADRs was 1.26.

Fig. 2 shows age-wise distribution of ADRs. The highest percentage of ADRs was found in adult age group 31–40 years, i.e., 377 (34.30%), more than 15 years of age (99%), and only 1% ADRs in age group <15 years. According to the WHO-UMC causality assessment scale, all ADRs were probable. There was no any certain ADR that could be found out.

Fig. 3 shows system-wise distribution of ADRs among OPD patients. Skin was the most common organ showing highest number of ADR (41.87%), second highest is gastrointestinal tract system (34.31%), central nervous system ADRs were 13.55%, and other miscellaneous ADRs were 12.59 including respiratory, cardiovascular system, renal, hematological, and musculoskeletal system.

Fig. 4 shows department-wise frequency of ADRs among study patients. Internal medicine was the most common department (28.33%) ADRs, the second most common department was ART (20.05%), and rest of the department were skin (19.96%), tuberculosis (TB) chest (10.02%), and psychiatry (7.35%).

Fig. 5 shows a common group of medicines causing ADRs. Drug-wise distribution of ADRs was antimicrobials (22.24%), analgesic (19.91%), ART (12.92%), anti-TB (9.74%), antipsychotic medicines (8.05%), antidiabetic medicines (7.83%), antiepileptic medicines (7.20%), antihypertensive medicines (5.93%), calcium (4.46%), and folic acid (4.23%).

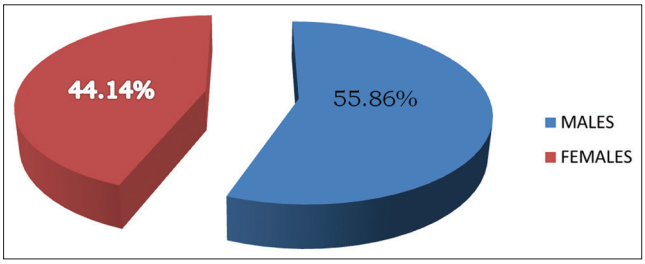

Fig. 1: Gender-wise distribution of adverse drug reactions

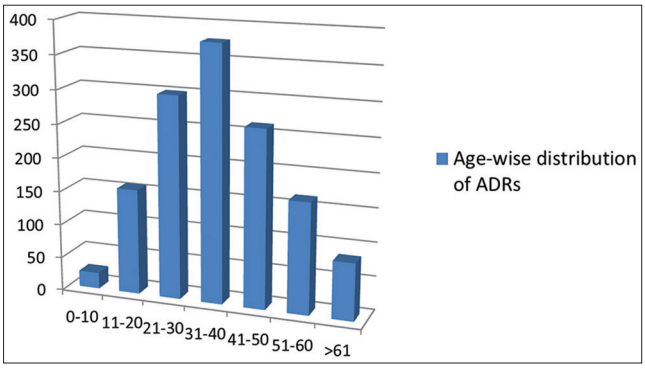

Fig. 2: Age-wise distribution of adverse drug reactions

Fig. 6 shows antimicrobials causing ADR. In the present study, of total AMAs causing ADRs (195), maximum number of ADRs were due to amoxicillin+clavulanic acid, i.e., 48 (24.61%), followed by amoxicillin 44 (22.56%), ciprofloxacin 26 (13.33%), and cotrimoxazole 21 (10.76%).

Fig. 7 shows the most common medicines causing ADRs. Most common medicines causing ADRs were efavirenz 85, diclofenac sodium 61, amoxicillin+clavulanic acid 59, and rifampicin 44.

Table 1 shows symptom-wise classification of ADRs. In this study, common symptoms due to ADRs of medicines were itching 174 (15.83%), skin rash 108 (9.82%), gastritis 104 (9.46%), headache 72 (6.55%), and vomiting 68 (6.18%).

Fig. 8 shows Hartwig–Siegel severity scale. 72.70% were mild reactions, 26.93% were moderate reactions, and 0.36% were severe ones. There were three serious ADRs, two Stevens–Johnson syndrome due to nevirapine and carbamazepine and third anaphylactic reaction due to injection ceftriaxone.

Table 2 shows modified Thornton and Schumock preventability scale. 51.95% reactions were not preventable, whereas 40.85% reactions were possibly preventable.

DISCUSSION

In the present study, a total of 1099 ADRs were documented from a tertiary teaching care hospital of Central India. In this study, males experienced a significantly higher percentage of ADRs than females, a finding consistent to Shamna *et al.* [11]. Most of the patients in our study were in the age group of 31–40 years, whereas in Ramakrishnaiah *et al.*, study most of the patients were in the age group of 41–60 years [5]. Distribution of ADRs according to the WHO-UMC causality assessment scale [10] showed that all ADRs were probable and none as a certain. Maximum ADRs were due to AMAs, a finding consistent with other studies [4]. This shows the importance of physician's awareness to AMA-

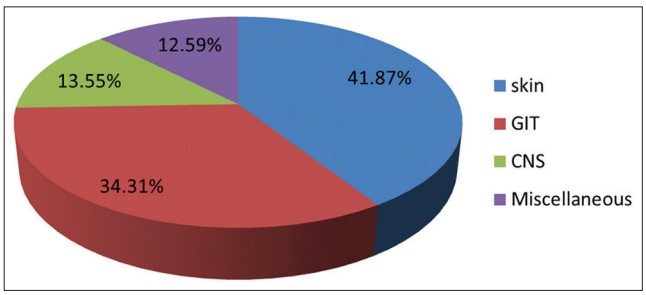

Fig. 3: System-wise distribution of adverse drug reactions

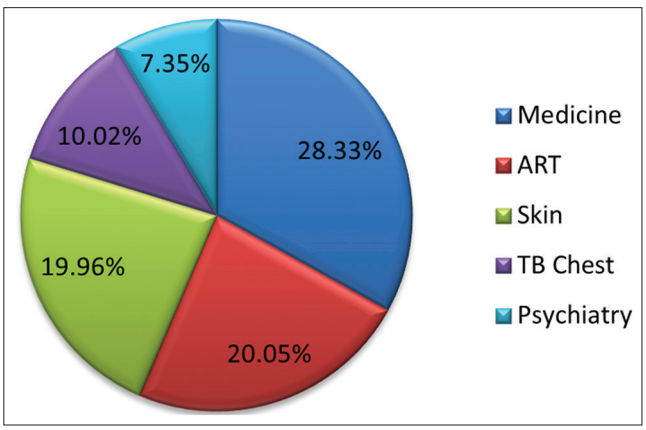

Fig. 4: Department-wise frequency of adverse drug reactions

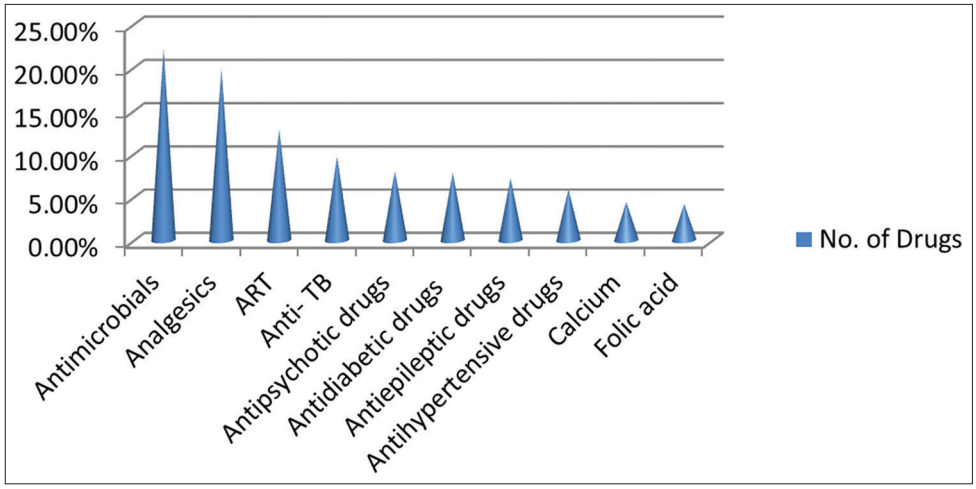

Fig. 5: Common group of medicines causing adverse drug reactions

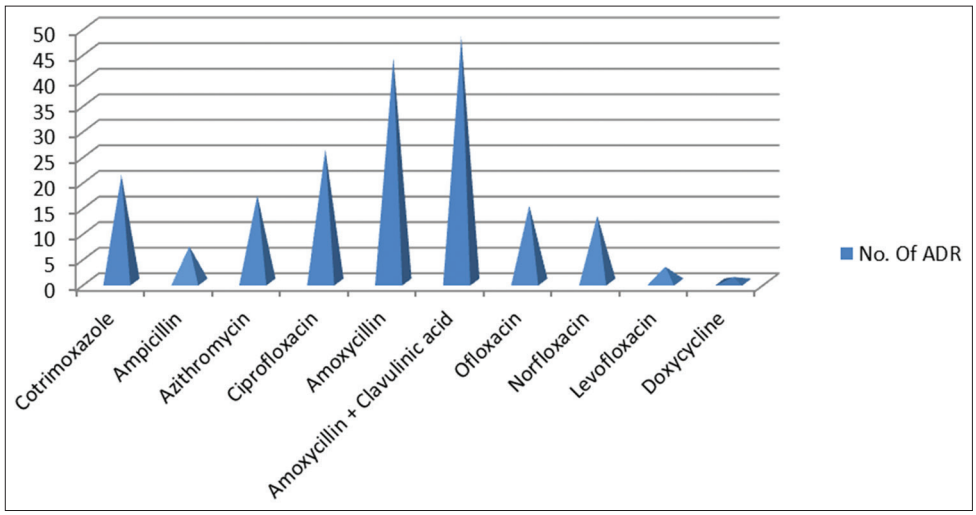

Fig. 6: Common antimicrobials causing adverse drug reactions

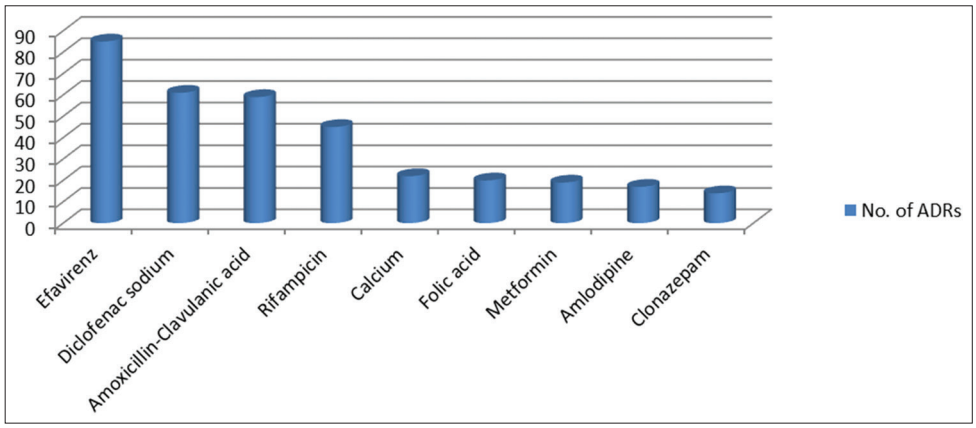

Fig. 7: Most common medicines causing adverse drug reactions

related ADRs in daily life. Since the ADR manifestation may be similar with the disease course and increase the unnecessary investigations and results in undue delay to proper and rational treatment.

Among the various systems affected by ADRs, skin is the most common system showing 41.87% of ADR cases as it is the biggest organ in the body and GIT is the next system to affect in 34.31% of ADR cases as majorityof medicines are given througoral route and CNS in 13.55% of ADR cases as few medicines cross blood brain barrier. This finding is similar to Indian studies [11,12].

Among the various departments reporting ADRs, medicine is the most common department (28.33% ADRs) [11]; next, departments to report ADRs were ART (20.05%), skin (19.96%), and TB chest (10.02%).

All these departments are allied to medicine and the treatment line is based on the medications only so these departments report maximum number of ADRs than surgical departments where surgery is the main treatment. Departments such as ART, skin and TB include chronic infectious conditions which require the use of combination of medicines for prolonged duration. Increase in number of drugs per prescription increases the chances of drug interaction and leads to causation of ADR increasing the morbidity and mortality and cost of drug treatment. The attributable financial burden of drug-related morbidity and mortality is around Rs. 690 (US $15) per ADR [13]. In this study, the most common group of medicines causing ADRs was AMAs, analgesics, ARTs, anti-TB, antipsychotic, antidiabetics, antiepileptic, and antihypertensives. Amoxicillin-clavulanic acid (45%) was the most common antimicrobial used followed by amoxicillin (42%). Majority of patients treated in hospitals received at least one antibiotic and a significant proportion of them either receive two or more which leads to increased chances of ADRs in patients [14]. According to modified Hartwig and Siegel severity scale, 72.70% were mild reactions majority consisted that of itching, diarrhea, and metallic taste, 26.93% were moderate reactions such as drug eruptions, some cases of pain in abdomen, and angioedema, and 0.36% were severe reactions which included immediate hospitalization and prompt treatment. A severe ADR is "any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening [15]." Two cases were of Steven–Johnsons syndrome due to nevirapine and carbamazepine, and a case was of anaphylactic shock due to injection ceftriaxone. Shamna *et al*. showed 8% of severe reactions, whereas it was 5% for Yerramilli *et al*. [16]. According to modified Thornton and Schumock preventability assessment scale, 64.28% reactions were not preventable in pediatric age group as oppose to De Las Salas *et al*., whereas 98.7% were not preventable in children [17]. Non-preventable reactions may be non-predictable and may occur after a single dose, caused by immunological abnormality (drug allergy), inherited genetic abnormalities (idiosyncrasy). Measures to decrease the severity of the non-preventable ADRs are the use of proper resuscitative measures and apt supportive measures and quick identification of ADR that is by taking appropriate drug history, studying patient's case records, selecting alternative drug with different chemical structure, and symptomatic treatment of the patients. Sensitivity tests must be performed while using penicillins, ester-linked local anesthetics, various anti-seras such as ATS, ADS, and ASV, and iodine-containing radio-contrast media. In our study, 45.40%

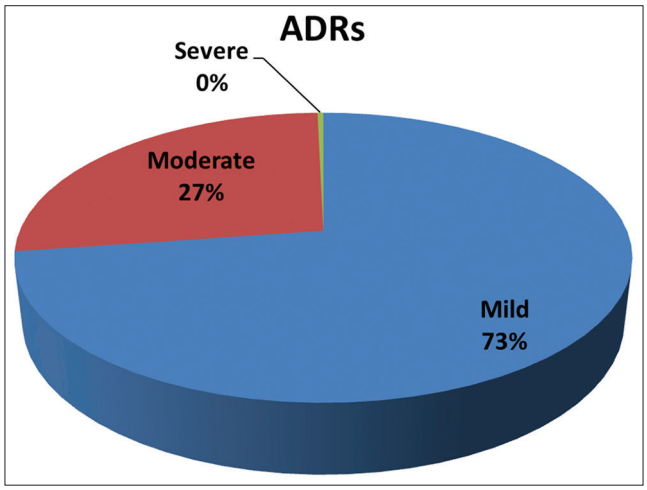

Fig. 8: Hartwig-Siegel severity assessment scale

Table 1: Symptom-wise classification of ADRs

S. No.	Symptom	Number of ADRs (%)
1	Itching	174 (15.83)
2	Skin rash	108 (9.82)
3	Gastritis	104 (9.46)
4	Headache	72 (6.55)
5	Vomiting	68 (6.18)
6	Nausea	43 (3.91)
7	Anemia	43 (3.91)
8	Constipation	43 (3.91)
9	Mouth ulceration	41 (3.73)
10	Diarrhea	33 (3)
11	Drug eruption	33 (3)
12	Disorientation	32 (2.91)
13	Joint pain	24 (2.18)
14	Acne	21 (1.91)
15	Gynecomastia	16 (1.45)
16	Pain in abdomen	16 (1.45)
17	Metallic taste	15 (1.36)
18	Dry mouth	12 (1.09)
19	Angioedema	8 (0.72)
20	Giddiness	8 (0.72)
21	Weight gain	2 (0.18)
22	Anaphylactic shock	2 (0.18)
23	Steven–Johnson syndrome	2 (0.18)

ADRs: Adverse drug reaction

Table 2: Modified Thornton and Schumock preventability scale

Age-group	Definitely preventable (%)	Possibly preventable (%)	Non-preventable (%)
Pediatric (up till 12 years)	0	10 (0.9)	18 (1.63)
Adult (13–60 years)	76 (6.91)	399 (36.3)	498 (45.31)
Geriatric (>60 years)	3 (0.27)	40 (3.63)	55 (5)
Gender			
Male	50 (4.54)	261 (23.74)	158 (14.37)
Female	29 (2.63)	188 (17.1)	413 (37.57)

of reactions were possibly preventable, whereas Tiwari *et al.* quoted 5% reactions in this category [18]. These can be minimized by routinely monitoring the patients, by early diagnosis, and by best possible drugs with different group. Patients should be kept under strict surveillance when prescribed with notorious medicines such as oral anticoagulants and oral hypoglycemics and drugs with narrow therapeutic index and medicines affecting the vital functions.

CONCLUSION

Majors that help to minimize the ADRs are proper and essential laboratory monitoring, genetic testing (G6PD deficiency and human leukocyte antigen testing), patient education for any untoward or any undesired symptom or reaction so that they actively report at the earliest, early recognition, and reporting of ADR. Dying from disease is sometimes acceptable, but dying from drug is never acceptable, so culture should be cultivated to report ADRs. Awareness regarding reporting of ADRs among all health-care professionals, patients, and their relatives is of utmost importance. In the era of modern medicine, the patient should be treated with the optimal use of medicines as medicines are very hands of Gods if they are used prudently.

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